Leptin and energy expenditure

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Purpose of review

A fundamental advance in our understanding of endocrine control of energy balance and body weight came with the discovery of the adipocyte-derived hormone leptin. The leptin pathway appeared to be the long-sought peripheral signal pathway from the adipose tissue to the brain involved in the regulation of feeding and energy balance.

Recent findings

Initially, leptin was considered to function as the long-sought antiobesity hormone. According to this hypothesis, rising concentrations of leptin with increasing adiposity would generate a signal to reduce food intake and increase energy expenditure in order to limit further weight gain. However, widespread resistance to the proposed antiobesity action of leptin is observed in humans, which might reflect the fact that the inability to store energy efficiently at times of abundance is evolutionarily disadvantageous. According to this alternative view, falling leptin concentrations observed during fasting act as a peripheral signal of starvation, which serves to conserve energy in the face of limited reserves. However, leptin administration failed to blunt the changes in energy expenditure during severe energy restrictions in several clinical studies. In addition, leptin therapy in several different human low-leptin states failed to affect energy expenditure in recent studies.

Summary

Increasing evidence from human studies suggests that leptin predominantly influences the human energy balance through appetite but appears not to be involved in regulating energy expenditure. None of the expected factors such as resting metabolic rate, total diurnal energy expenditure or dietary induced thermogenesis was related to blood leptin concentrations.

Keywords

appetite, energy expenditure, human, leptin

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Abbreviations

PEG-OB	pegylated human recombinant leptin
SNS	sympathetic nervous system

1363-1950

Introduction

The discovery of the hormone leptin (also known as OB protein) by Zhang and colleagues in December 1994 had an enormous impact both in understanding the molecular control of energy balance and in attitudes to the scientific study of obesity [1]. Over the last 9 years more than 4500 papers have been published on leptin (from the Greek leptos, meaning thin), leading to an ever-advancing body of knowledge. The leptin pathway appeared to be the long-sought peripheral signal pathway from the adipose tissue to the brain involved in the regulation of feeding and energy balance.

In 1950, a spontaneous recessive genetic mutation resulting in profound obesity and diabetes was identified in an inbred mice colony [2]. Shortly after the discovery of the *ob*/*ob* mouse, additional recessively inherited forms of obesity, called the diabetes (*db*/*db*) mouse and the Zucker (*fa*/*fa*) rat were described [3,4]. Despite being genetically different, these animals expressed phenotypically identical characteristics, such as massive obesity of early onset due both to hyperphagia and reduced energy expenditure. In addition, these rodents exhibited hypothermia, type 2 diabetes, dyslipidemia, hypercortisolemia, decreased immune function and infertility due to hypogonadotropic hypogonadism. In the 1970s, classic parabiosis experiments, in which the circulations of *ob*/*ob* and *db*/*db* mice were connected, resulted in weight loss due to hypophagia and finally cachexia and death in the *ob*/*ob* mouse, while retention of increased food intake and weight in their *db*/*db* pair-mates was observed [5,6]. These results led to the hypothesis that the *ob* gene encoded a circulating substance that affected the energy balance and consequently body weight control. Also, it was suggested that the receptor of this unknown substance was encoded by, or under control of, the *db* gene. It was not until 1994 that this hypothesis could be verified and a new endocrine system was revealed.

Leptin, an antiobesity hormone?

Soon after the cloning of the *ob* gene, leptin-deficient *ob*/*ob* mice were injected with recombinant leptin, which led to weight loss due to decreased food intake and increased energy expenditure [1,7–9]. This outcome supported the original concept that leptin's function was to control weight gain by reducing food intake and increasing energy expenditure as its concentration in blood rises with increasing adiposity. This impressive

effect of leptin administration to *ob/ob* mice raised expectations that human obesity could also be a (relative) leptin-deficient state that could possibly be treated with exogenous leptin. Several early population studies, however, failed to demonstrate mutations in the human gene encoding for leptin [10–12]. In contrast, after the development of radioimmunnoassays for human leptin, it became clear that in the majority of obese individuals elevated serum leptin levels are found [13], which apparently failed to prevent obesity. From these results, the hypothesis of leptin resistance or reduced sensitivity to leptin in human obesity emerged, comparable to insulin resistance in type 2 diabetes [14,15]. The observation that higher doses of recombinant leptin are required to affect feeding behavior, metabolism, and body fat in diet-induced obese mice compared with normal mice supported this concept of leptin resistance [9]. These early results suggested the possibility that high therapeutical doses of human recombinant leptin may be able to overcome the presumed increased leptin resistance present in obese individuals and result in reduction in body weight by reducing food intake and increasing energy expenditure.

To test this hypothesis, we studied the effect of weekly administration of long-acting pegylated human recombinant leptin (PEG-OB) on body weight loss and energy expenditure in obese men during mild hypocaloric conditions for 12 weeks. Treatment with PEG-OB sustained elevated levels of both PEG-OB and endogenous leptin and increased post-absorptive satiety throughout the treatment period without an effect on weight loss [16]. Despite sustained elevated levels of both PEG-OB and leptin throughout the treatment period, no effect was observed on weight loss or energy expenditure measured by a respiration chamber [17]. This outcome was in line with the results of several other clinical studies which showed that even supraphysiological leptin concentrations failed to significantly affect body weight in humans during weight maintenance or mild hypocaloric conditions [18,19]. In particular, no effect was observed on energy expenditure measured by indirect calorimetry [18]. Thus, it is unlikely that in humans leptin plays a role analogous to that observed in rodents, in which it is involved in acute and chronic adaptation of energy intake and energy expenditure.

Leptin, a starvation hormone?

The outcome of these clinical studies demonstrated that high leptin concentrations failed to significantly affect body weight, which implicates that humans are highly leptin resistant. This observation was, however, consistent with an alternative view of the physiological role of leptin, which emerged in 1998 [20,21]. The group of Flier hypothesized that the widespread occurrence of leptin resistance [22–24] might reflect the fact that the inability to store energy efficiently at times of abundance is evolutionarily disadvantageous. These investigators postulated that the falling concentration of leptin during starvation and its effects may constitute part of the thrifty genotype, a set of genes thought to promote survival during periods of insufficient energy intake in human evolution by increasing the efficiency of energy storage. The fact that during starvation leptin levels drop rapidly and out of proportion to body adiposity changes appears to support this hypothesis [25,26]. In this updated thrifty genotype concept, the drop in leptin concentrations during periods of limited energy intake might signal the brain to initiate the complex neural, metabolic, neuroendocrine, and behavioral responses thought to have survival value in periods of inadequate energy intake. In addition, this concept suggests that an effective adipostatic role of leptin would subvert the thrifty genotype by limiting the capacity of energy storage during periods of abundance, which would result in reduced survival in subsequent periods of food shortages. Stated differently, evolution would favor resistance to leptin action (leptin resistance) when leptin concentrations are rising or high during periods of sufficient energy intake/storage. Furthermore, they speculated that the shape of the biological dose–response curve of leptin may depend on the conditions in which a certain species evolved.

An important clue suggesting that leptin might be involved in the regulation of the adaptations during starvation emerged with the observation that leptin-deficient *ob/ob* mice possess many characteristics similar to those during starvation. The genetically obese *ob/ob* mouse, which lacks leptin, exhibits all adaptive physiological mechanisms appropriate for food scarcity even when it has free access to food [21]. The administration of leptin reversed these adaptations, such as low body temperature (topor), reductions in thyroid function and sympathetic nervous system (SNS) activity, hence raising energy expenditure. A classic replacement study preventing the characteristic fall in leptin during fasting blunted the activation of these neuroendocrine axes and also prevented hypothermia which also increased energy expenditure [27,28]. However, leptin treatment of normal mice fed ad libitum only prevents the decrease in energy expenditure that would normally occur with the leptin-induced reduction in food intake [29].

An indication suggesting that leptin could play an important role in the recognition of an early derailment of energy homeostasis and additional physiological functions such as reproduction can be derived from some observational studies in athletes. So far studies evaluating whether exercise per se or energy deficiency is the critical factor in the regulation of leptin is limited.

Van Aggel-Leijssen *et al.* [30] showed that acute exercise decreased the nocturnal peak and average 24 h plasma leptin concentration. Positive or negative energy balance gave a much higher fluctuation. A short-term training program (12 weeks) did not influence leptin levels corrected for changes in fat mass [31]. In a long-term training program (16 months), however, a significant inverse relation was found between leptin levels and hours of training corrected for changes in insulin and body fat percentage [32]. In an elegant designed study, Hilton and Loucks [33] dissected the exercise stress from the energy availability. Low-energy availability profoundly suppressed the 24 h amplitude of the diurnal rhythm of leptin when exercise had no effect. The effect of low-energy availability caused by increased exercise energy expenditure was smaller than that caused by dietary restriction. The study demonstrated the importance of energy availability in comparison to exercise stress on leptin as an important biomarker of energy homeostasis.

The hypothesis proposed by Flier *et al.* provided an explanation for the ineffectiveness of a high-dose PEG-OB in our obese individuals on a mild hypocaloric diet as well for the fairly moderate results of the Heymsfield trial [19]. Furthermore, an extension of this hypothesis is that exogenous leptin should affect energy regulation when administrated during severe energy restriction. Therefore, to test this hypothesis, we executed another randomized, double-blind, and placebo-controlled study to investigate whether elevated leptin levels using PEG-OB affected weight loss, changes in energy expenditure, and appetite, during semistarvation induced by a very low calorie diet in healthy overweight male volunteers. Weekly subcutaneous administration of PEG-OB led to significant additional weight loss and reductions in appetite after 6 weeks of treatment and severe energy restriction, but did not affect changes in energy expenditure measured by indirect calorimetry [34•].

In contrast to rodents, exogenous leptin in our study did not prevent or blunt the physiological fall in energy expenditure, which normally occurs during food deprivation. Two major factors reducing energy expenditure during fasting are the inhibition of SNS activity and the drop in thyroid hormones. Both fasting-induced effects were blunted in rodents treated with leptin [27,35]. Moreover, administration of leptin directly into the brains of rhesus monkeys acutely activated the SNS, suggesting that leptin may also influence energy expenditure in these nonhuman primates [36]. The fact that PEG-OB administration did not disinhibit SNS activity or prevent the fall in thyroid hormones might account for the absence of a stimulatory effect on energy expenditure in this human study [37]. In agreement with our findings, recombinant replacement therapy during short-term starvation in healthy men did not significantly alter the changes in energy expenditure [38•]. Another study, however, reported a reversal of the effects of sustained weight reduction on energy expenditure by a low dose of exogenous leptin [39].

Leptin replacement in human leptin-deficiency states

The findings of this study are consistent with the characteristics of homozygous human patients with total leptin deficiency or nonfunctional leptin receptors. These rare and very obese individuals have been shown to have a normal core temperature and normal resting energy expenditure but are markedly hyperphagic [40–43]. In addition, mice heterozygous for the *ob* gene [44,45] and individuals who are genetically partially deficient in leptin [46] appear to be associated with an intermediate phenotype. Daily subcutaneous human recombinant leptin treatment of three children with a mutated *ob* gene caused rapid and progressive reductions in body weight. This weight loss was mainly due to reductions in food intake as a result of decreased appetite and food-seeking behavior. However, leptin therapy in two congenital leptin-deficient children failed to affect basal metabolic rate or free-living energy expenditure (measured using doubly labeled water) who were both adjusted for lean body mass [47].

Several other syndromes have been associated with very low leptin levels. Recently, two siblings with Rabson-Mendenhall syndrome (severe insulin resistance and presumed insulin receptor mutations and low leptin levels) were treated with recombinant human leptin for 10 months. Resting energy expenditure (and lean body mass) remained stable during leptin treatment [48•].

Leptin-replacement therapy in patients with lipodystrophy and very low leptin levels has led to a decrease in resting metabolic rate most likely secondary to weight loss [49,50]. A major drawback of some studies, however, is the fact that the changes in energy expenditure are not adjusted for changes in lean body mass over the treatment period.

Conclusion

In summary, in humans, increasing evidence to date suggests that leptin predominantly influences the human energy balance through appetite but appears not to be involved in regulating energy expenditure. Both animal and human studies indicate that low or falling leptin levels (as observed during fasting) act as a peripheral signal of starvation, which subsequently increases appetite thereby ensuring survival of the species. At the other end of the spectrum, resistance to the proposed antiobesity action of high or rising leptin levels is

observed in both animals and humans. Contrary to rodents, even supra-physiological leptin concentrations reached during several clinical trials failed to affect the human energy balance including energy expenditure. This widespread occurrence of leptin resistance could reflect the fact that the inability to store energy efficiently at times of abundance is evolutionarily disadvantageous.

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